Review Article

Innovative Insights in Digital Health

The Stochastic Variability in Drug Response: Role of Molecular Noise

Manjula MJ[1]*, Jyothsnya S[2] and Divyashree CR[3]

[1]Assistant Professor, Department of Pharmacology, Rajarajeswari Medical College and Hospital, Affiliated to Dr M.G.R Educational and Research Institute University, Karnataka, India.

[2]Professor, Department of Pharmacology, St. Peter's Medical College and Hospital, Hosur, India.

[3]Assistant Professor, Department of Pharmacology, Mansarovar Medical College and MGU Hospital, Bhopal, India.

Received Date: 30 Jan 2026;
Accepted Date: 22 Mar 2026;
Published Date: 30 Mar 2026.

***Correspondence:** *Dr. Manjula MJ, Assistant Professor, Department of Pharmacology, Rajarajeswari Medical College and Hospital, Affiliated to Dr M.G.R Educational and Research Institute University, Karnataka, India.*

Citation: Manjula MJ, Jyothsnya S, Divyashree CR. The Stochastic Variability in Drug Response: Role of Molecular Noise. Innov Insights Digit Health. 2026; 2(1): 1-3.

ABSTRACT

Although we prescribe the same medication for patients with similar diagnoses and disease patterns at the molecular level, drug responses may often show significant variation in efficacy, effectiveness, and predictability of outcomes. On various theoretical as well as clinical backgrounds, while the genetic and environmental factors confirm this theory to some extent, recent advances in systems biology and enhanced conceptualization in cell signalling technologies have highlighted the role of stochastic processes, especially the molecular noise, as a critical determinant.

This review article briefs the nature, origin, and implications of the role of molecular noise in drug response. This further explains the integrated findings from single-cell analyses, theoretical modelling, and confirmed clinical scenarios across various therapeutic sections. Based on the available data, the Intrinsic and extrinsic noise contribute to heterogeneity in signal transduction, gene expression, and the behaviour of the receptor, which ultimately affects the therapeutic outcomes. Also, understanding the possibility of artificial intelligence and advanced technologies for analyzing the molecular anchoring of the cell, its protein layer, and the organelle, the concept of stochastic variability will be incorporated into everyday clinical practice sooner, with better outcomes.

***Keywords:** Molecular anchoring, cell signalling, Stochastic Variability, receptor behaviour*

Introduction

The variability in drug response has always been a complex scenario in the context of clinical pharmacology and drug therapeutics. Generally, it was considered to be due to the pharmacogenetic variation, associated metabolic changes, gene polymorphisms, and other associated environmental factors. Nevertheless, even after adjusting all these parameters, the substantial variability of drug response is observed in a few patients. This might be due to the function of a stochastic element, which is a natural feature of biological systems [1,2].

The concept of molecular noise, which is a function of the stochastic nature of biological processes such as gene expression and protein-protein interactions, key player. In this context, we are interested in understanding the origin of this noise and how this impacts the variability of drug response.

Defining Molecular Noise and Stochasticity in Biology

Molecular noise is generated from cellular systems via intrinsic and extrinsic factors. There is a chance that biochemical reactions in cells can be a source of molecular noise, as the occurrences of many of these will be random in terms of when they occur.1 Examples of molecular noise include gene transcription occurring randomly and the binding of one molecule randomly to another.

Extrinsic noise is how the external environment is associated with random or unreliable ways to produce results in a gene/pathway that is not of interest. There are two ways to define extrinsic noise. First, by examining the properties of the environment in which cells are found (such as volume, total ribosomes) and by measuring variability within the microenvironments of the cells. Intrinsic and Extrinsic noise may affect the way a cell responds to drugs positively or negatively [2,3].

Modelling Stochastic Processes

Stochastic modelling is a demonstrated method to model how stochastic processes occur using stochastic models of biological systems. Specifically, the Gillespie algorithm and Stochastic Differential Equations can be used to review and understand how molecular fluctuations affect biological systems.4 The findings show that simple gene regulatory networks can produce highly complex, nonlinear, bimodal drug responses due to intrinsic and extrinsic noise. In addition, toggle systems and feedback loops are particularly sensitive to noise; therefore, an all-or-nothing drug response would result [4,5].

Experience With Molecular Noise in Drug Response

The use of single-cell technologies (single-cell RNA sequencing [scRNA-seq], flow cytometry, and mass cytometry) to quantify molecular noise is becoming the new “gold standard” and has only recently been developed. As such, the evidence in the literature is increasing that drug transporters and metabolizing enzymes demonstrate vast variability in their expression levels at the single-cell level [3,6].

Yoon BJ et al proposed an algorithm and compared it with the existing Gur Game algorithm, which explained the mechanism behind the concentration change of a specific drug that affects the overall drug response, which further helps in estimating and optimizing the concentration for better pharmacological response [7].

Variability in Signal Transduction

Stochastic fluctuations in signalling molecules like ERK, AKT, or NF-κB can lead to different cellular outcomes in response to the same drug stimulus. In T cells, for instance, differences in T-cell receptor (TCR) signalling strength caused by noise can create various activation states, affecting the effectiveness of immunotherapy. Molecular Noise and Drug Resistance: Non-genetic Heterogeneity in Cancer. A striking example of noise-driven variability comes from cancer biology [3].

Non-genetic resistance occurs when cancer cells survive drug treatment without developing genetic mutations. This phenomenon has been linked to noise-induced changes in cell behavior. A group of “persister” cells can randomly enter a resting state and escape the harmful effects of chemotherapy. Bet-Hedging Strategies. Cells can use molecular noise as a survival strategy known as bet-hedging. In this approach, a genetically identical population behaves differently, making sure that some cells can withstand unexpected environmental challenges like drug treatment. This idea has been seen in bacterial persistence and is increasingly acknowledged in human cells [3,8].

Systems Biology Perspectives

Network Noise Propagation

Positive feedback loops are network motifs that identify how noise moves through cells. These patterns can make noise stronger or weaker. Based on these feedback loops, the molecular variation would be better understood, and the association with therapeutics could be explained well.

The distribution of a few specific patterns would increase noise, whereas others can reduce it. This is especially important to understand the fate of cells as a consequence of drug action. For example, the destruction of the cancer cells. If the cell signal noise is comparatively stronger, then the cell might not die.8 Farquhar KS et al. conducted a study by decoupling expression noise from mean protein levels through synthetic feedback regulation. They identified a dual role for stochasticity in the adaptation of the drug administered. In isogenic Chinese hamster ovarian cell models, positive-feedback-driven noise functioned as a flexible survival mechanism, enabling rapid adaptation to high Puromycin concentrations without requiring permanent genetic changes. This outcome was in contrast with low-noise negative-feedback systems, which necessitated the mutational evolution to survive. Understanding these noise-driven survival strategies provides critical insights into the non-genetic origins of chemoresistance and clinical relapse [9].

Robustness and Fragility

Human bodies are designed to balance being strong as well as flexible. The persisting pathways might make the noise either weaker or more sensitive, to adapt to the changed cellular environment. On administration of any medication, this balance might be affected. The magnitude of affected changes will be reflected as a change in the expected pharmacological outcome [3,8].

Clinical Implications of Molecular Noise

Personalized Medicine

The way of tailoring treatments to individuals based on their genes might not be enough because it does not take into account the random nature of cells. Looking at cells in tumors or immune cells can give us a better idea of how a person will respond to a drug because it takes into account the real-time differences between cells [10].

Biomarker Development

Understanding noise patterns can help us develop biomarkers. For instance, looking at the variability in the expression of PD-L1 among tumor cells can help us predict how well a person will respond to a drug better than just looking at the average levels [3].

Impacts on Dosing and Therapeutic Windows

Drugs that have a response to small changes in dose are particularly affected by noise. Modelling the effects of stochasticity can help us design dosing regimens that keep the drug levels within a safe range [10].

Case Studies

Oncology: Targeted Therapies

In melanoma patients with a mutation, treatment with BRAF inhibitors can lead to different responses in different parts of the tumor. Looking at cells has shown that noise in the MAPK pathway can create resistant cells even before treatment starts [9,10].

Immunology: CAR-T Cell Therapy

Variability in CAR expression and signalling in engineered T cells can affect how well they kill cancer cells. Noise in production and killing kinetics affects how consistent and long-lasting the treatment is.

Pharmacogenomics: CYP450 Enzymes

Although genetic differences in CYP450 enzymes explain a lot of the differences between people, random differences in enzyme expression within a single tissue or over time add another layer of complexity, affecting how drugs are metabolized and how toxic they are. Wang Z et al has detailed the Stochastic coupled Pk/PD model, clinical designs for implementing, the estimation tests, and also the computer simulation.

Strategies to Mitigate Noise Effects

- Targeting regulators to stabilize network behavior, like using kinase inhibitors.
- Using combination therapies to reduce reliance on noisy nodes.
- Designing synthetic biology tools, like noise-filtering gene circuits.
- Adaptive dosing that takes into account variability in response over time [3,8,10].

Future Directions

Combining single-cell data, stochastic modelling, and machine learning is an area of research. Predictive models that take into account noise signatures could soon be used in clinics to anticipate treatment outcomes or resistance. New technologies like transcriptomics and time-lapse microscopy will help us understand how molecular noise works in real tissues and over time. Bishnu SK et al used an artificial intelligence (AI) model for building a stochastic algorithm. In their study, a robust Random Forest Regression (RFR) model was developed to characterize the Sorption Enhanced Steam Methane Reformer (SE-SMR) and subsequently integrated into a Simulated Annealing (SA) optimization framework. Development of similar AI models to understand the drug-receptor-microenvironment noise would help in dose optimization [11,12].

Molecular noise is not a nuisance but a fundamental part of life at the cellular level. Recognizing its role in drug response variability opens up possibilities for precision medicine and therapeutic innovation. By combining models, single-cell analytics, and systems pharmacology, researchers and clinicians can better predict, manage, and exploit this variability for better patient outcomes. Molecular noise is a factor in how our bodies respond to drugs and understanding it can help us develop better treatments.

Conflict of Interest and Funding

The author declares no conflict of interest and received no specific funding for this work.

References

1. Elowitz MB, Levine AJ, Siggia ED, Swain PS. Stochastic gene expression in a single cell. Science. 2002; 297: 1183-1186.
2. Wang Z, Luo J, Fu G, Wang Z, Wu R. Stochastic modeling of systems mapping in pharmacogenomics. Adv Drug Deliv Rev. 2013; 65: 912-917.
3. Irurzun-Arana I, Rackauckas C, McDonald TO, Trocóniz IF. Beyond Deterministic Models in Drug Discovery and Development. Trends Pharmacol Sci. 2020; 41: 882-895.
4. Yadalam PK, Ardila CM. Stochastic gene expression modeling using the Gillespie algorithm: insights into oral cancer genomic variability. Braz Dent Sci. 2025; 28: e4804.
5. Raj A, van Oudenaarden A. Nature, nurture, or chance: stochastic gene expression and its consequences. Cell. 2008; 135: 216-226.
6. Altschuler SJ, Wu LF. Cellular heterogeneity: do differences make a difference? Cell. 2010; 141: 559-563.
7. Yoon BJ. Enhanced stochastic optimization algorithm for finding effective multi-target therapeutics. BMC Bioinformatics. 2011; 12: S18.
8. Shaffer SM, Dunagin MC, Torborg SR, Torre EA, Emert B, et al. Rare cell variability and drug-induced reprogramming as a mode of cancer drug resistance. Nature. 2017; 546: 431-435.
9. Farquhar KS, Charlebois DA, Szenk M, Cohen J, Nevozhay D, et al. Role of network-mediated stochasticity in mammalian drug resistance. Nat Commun. 2019; 10: 2766.
10. Tirupathi Rao P, Venkateswaran M, Vishnu Vardhan R. Stochastic modelling on drug efficacy in self-drug administration health problems. J Serv Sci Manag. 2011; 4: 491-498.
11. Keyl P, Keyl J, Mock A, Dernbach G, Mochmann LH, et al. Neural interaction explainable AI predicts drug response across cancers. NAR Cancer. 2025; 7: zcaf029.
12. Bishnu SK, Alnouri SY, Al Mohannadi DM. Stochastic algorithm-based optimization using artificial intelligence/machine learning models for sorption-enhanced steam methane reformer reactor. Comput Chem Eng. 2025; 196: 109060.